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BRIEF REPORTS

Cancer Chemotherapy Treatment Patterns and Febrile Neutropenia in the US Veterans Health Administration

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ABSTRACT

Background: The Veterans Health Administration (VHA) is the largest integrated health care system in the United States and a major cancer care provider. **Objective:** To use VHA database to conduct a population-based study of patterns of myelosuppressive chemotherapy use and to assess the incidence and management of febrile neutropenia (FN) among VHA patients with lung, colorectal, or prostate cancer or non-Hodgkin lymphoma (NHL). **Methods:** Data were extracted for the initial myelosuppressive chemotherapy course for 27,899 patients who began treatment in the period 2006 to 2011. FN-related costs were defined as claims containing FN diagnosis. **Results:** Most patients were men (98.0%); most were 65 years or older (55.8%). Patients received a mean 3.4 to 3.9 chemotherapy cycles/course (median cycle duration 34–43 days). The incidence of FN among patients with lung, colorectal, or prostate cancer or NHL was 10.2%, 4.6%, 5.4%, and 17.3%, respectively. Primary or secondary prophylactic antibiotics/colony-stimulating factors were received by 21% and 12% of patients, respectively. Antibiotics were more commonly given as primary or secondary prophylaxis for patients with lung, colorectal, and prostate cancer; colony-stimulating factors were more common for patients with NHL. Among patients with FN, those with lung cancer had the highest inpatient mortality (10%); patients with NHL had the highest costs ($24,571) and the longest hospital length of stay (15.4 days). **Conclusions:** VHA cancer care was generally consistent with National Comprehensive Cancer Network recommendations; however, compared with the general population, chemotherapy cycles were longer, combination chemotherapy was used less, and treatment to prevent FN was used less, differences that may be attributed to the unique VHA patient population. The impact of these practices warrants further investigation.

Keywords: chemotherapy, febrile neutropenia, supportive care, Veterans Health Administration.

Introduction

The Veterans Health Administration (VHA) is the largest integrated health care system in the United States and currently provides care for more than 5 million patients at hospitals, nursing homes, residential rehabilitation centers, and community- and facility-based clinics [1–4].

Compared with the general US population, patients within the VHA are more likely to be male, older, and have more comorbidities [4]. Despite differences in age and the prevalence of comorbidities, the incidence of cancer within the VHA is similar to the incidence of cancer among the US male population; the most common types of cancers are lung and bronchus cancer, colorectal cancer (CRC), and prostate cancer [5,6].

Cancer is commonly treated with myelosuppressive chemotherapy, and neutropenia is a common, dose-limiting adverse effect [7]. Neutropenia with fever (febrile neutropenia [FN]) can be life-threatening and often requires immediate hospitalization and treatment with intravenous antibiotics [8,9]. FN is associated with increased inpatient mortality, lengthy hospital stays, and significant costs [8,10–12].

The VHA maintains a fully integrated claims database that combines inpatient, outpatient, pharmacy, laboratory, and electronic medical records [2]. We used this database to conduct a population-based study of patterns of myelosuppressive chemotherapy use and to assess the incidence and management of FN among VHA patients with lung cancer, CRC, prostate cancer, or non-Hodgkin lymphoma (NHL).

Methods

Database

The VHA database includes records for more than 5 million patients, organized into 22 Veterans Integrated Service Networks,

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which combine data into a data warehouse based on geographic region.

Study Source Population

Patients who initiated one or more course of myelosuppressive chemotherapy between January 1, 2006, and September 30, 2011, were included. The index date was the date of chemotherapy administration in the first chemotherapy cycle. Patients were 18 years or older on the index date, continuously enrolled in the VHA health plan for 90 days or more before the index date, and diagnosed with lung cancer, CRC, prostate cancer, or NHL within 30 days of the index date. Cancer type was defined by two or more medical claims 7 or more days apart with the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes: lung cancer (162), CRC (153, 154), prostate cancer (185), or NHL (200, 202). For patients who received more than one course of chemotherapy during the study period, only the first course was evaluated. The follow-up period was the time from the index date to either the end of follow-up or death.

Patients were excluded if they received myelosuppressive chemotherapy or had a diagnosis of FN during the 90-day preindex period, had two or more primary cancers (*ICD-9-CM* codes 140.x-195.x, 199.x-209.x, 235.x-238.x), or had a medical claim for a hematopoietic bone marrow or stem cell transplantation (*ICD-9-CM* code 41.0 or Healthcare Common Procedure Coding System codes S2150, 38240-38242) during the study period.

Outcomes

Chemotherapy treatment patterns

For each patient, each cycle was identified within the first chemotherapy course (defined as starting on the index date and ending on the first day of the next cycle). Patients were excluded if the between-cycle interval was less than 7 days. If the second cycle had not commenced before day 60, both the cycle and the course of chemotherapy were considered complete 60 days after the index date. Subsequent cycles were similarly defined, up to a maximum of nine cycles. Outcomes were measured during the follow-up period, inclusive of the index date.

Febrile neutropenia

Based on data from previously published studies [13,14], patient-level FN incidence was approximated from inpatient or outpatient claims with a diagnosis of neutropenia (*ICD-9-CM* 288.0). Burden of FN included inpatient mortality (number of deaths divided by the number of patients admitted), hospital length of stay (LOS; based on relevant admission and discharge dates), and mean health care costs (calculated per patient per cycle, with FN adjusted to 2010 US dollars using the Consumer Price Index component for medical care). FN-related costs were defined as claims containing FN as the primary or secondary diagnosis and included FN-related outpatient, inpatient, prescription, and total medical (outpatient + inpatient + pharmacy) costs.

Supportive care

Use of corticosteroids, antihistamines, and antiemetics per cycle was defined as one or more pharmacy claim. Administration of colony-stimulating factors (CSFs) (filgrastim, pegfilgrastim, or sargramostim) and/or antibiotics was characterized as prophylactic or reactive use on the basis of the timing of use relative to the administration of chemotherapy. CSF or intravenous antibiotic prophylaxis was defined as first administration within 5 days of chemotherapy initiation in any cycle. Oral-antibiotic prophylaxis was defined as the first reported prescription fill up to 1 week before and up to 6 days after the receipt of chemotherapy. Primary prophylaxis, secondary prophylaxis, and reactive use were defined as prophylaxis beginning with cycle 1, prophylaxis beginning with cycle 2 or subsequent cycles, and no prophylaxis, respectively. Administration of intravenous antibiotics at the same time as an encounter for FN was classified as reactive use, even if FN occurred within 5 days of chemotherapy initiation [15–19].

Other variables measured included demographic characteristics (age, sex, Charlson Comorbidity Index) and history of anemia, other blood disorders, infection, or cancer as assessed by relevant *ICD-9-CM* codes. The presence of comorbidities was assessed during the 90-day preindex period.

Statistical Analyses

Descriptive analyses were used to summarize all study variables. Means and standard deviations are provided for continuous variables and numbers and percentages for categorical variables.

Results

Patients' Demographic and Clinical Characteristics

This study included 27,899 patients: 42.0% with lung cancer, 23.5% with CRC, 19.1% with prostate cancer, and 15.5% with NHL. Their demographic and clinical characteristics are presented in Table 1.

Chemotherapy Regimens

The five most common myelosuppressive chemotherapy agents used to treat each tumor type were carboplatin/paclitaxel (36.3%), carboplatin/etoposide (7.2%), cisplatin/etoposide (6.8%), carboplatin/pemetrexed (4.4%), and pemetrexed (3.9%) for lung cancer; capecitabine (37.5%), oxaliplatin (21.0%), fluorouracil (9.3%), capecitabine/oxaliplatin (6.3%), and mitomycin (4.9%) for CRC; docetaxel (41.7%), mitomycin (13.0%), methotrexate (10.3%), bevacizumab (5.6%), and hydroxyurea (3.7%) for prostate cancer; and rituximab (20.5%), cyclophosphamide/doxorubicin/rituximab (13.7%), cyclophosphamide/doxorubicin/vincristine/rituximab (8.1%), cyclophosphamide/rituximab (7.0%), and cyclophosphamide/vincristine/rituximab (4.3%) for NHL. Patients received a mean ± SD of 3.6 ± 2.4, 3.9 ± 3.0, 3.4 ± 2.9, and 3.9 ± 2.5 cycles for lung cancer, CRC, prostate cancer, and NHL, respectively, and the mean ± SD cycle duration was 39 ± 15, 40 ± 16, 44 ± 15, and 39 ± 14 days, respectively.

FN Incidence

The incidence of FN during the first chemotherapy course was 10.2%, 4.6%, 5.4%, and 17.3% for lung cancer, CRC, prostate cancer, and NHL, respectively (Table 2). For patients with NHL and lung cancer, the incidence of FN was highest in cycle 1 and decreased over subsequent cycles, whereas for those with prostate cancer and CRC, the incidence of FN was relatively similar across chemotherapy cycles (see Appendix Fig. 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.06.009).

Except for patients with NHL, the management of FN was split evenly between inpatient and outpatient settings; a higher proportion of patients with NHL were treated in the inpatient setting (Table 2).

Supportive Care

The use of corticosteroids, antihistamines, and antiemetics was higher in certain tumor types. The use of corticosteroids and antiemetics was highest in patients with lung cancer (many received platinum-containing chemotherapy), and the use of antihistamine was highest in patients with NHL (Table 2). Use in subsequent cycles was similar to that in cycle 1 (data not shown). Overall 21% of the patients received prophylactic

Table 1 – Patients' demographic and clinical characteristics at baseline.

Characteristic	Lung cancer (N = 11,715)	CRC (N = 6549)	Prostate cancer (N = 5322)	NHL (N = 4313)	Total population (N = 27,899)
Age (y), n (%)					
18–25	0 (0.0)	3 (0.1)	0 (0.0)	4 (0.1)	7 (0.0)
26–34	3 (0.0)	20 (0.3)	0 (0.0)	22 (0.5)	45 (0.2)
35–54	920 (7.9)	684 (10.4)	112 (2.1)	467 (10.8)	2183 (7.8)
55–64	4788 (40.9)	2576 (39.3)	1189 (22.3)	1545 (35.8)	10098 (36.2)
≥65	6004 (51.3)	3266 (49.9)	4021 (75.6)	2275 (52.8)	15566 (55.8)
Sex, n (%)					
Male	11429 (97.6)	6375 (97.3)	5322 (100.0)	4203 (97.5)	27327 (98.0)
Female	286 (2.4)	174 (2.7)	0 (0.0)	110 (2.6)	572 (2.1)
Charlson Comorbidity Index, mean ± SD	5.3 ± 3.5	5.1 ± 3.4	4.6 ± 3.1	3.7 ± 2.6	4.9 ± 3.3
History of other conditions, n (%)					
Anemia	723 (6.2)	707 (10.8)	265 (5.0)	291 (6.8)	1986 (7.1)
Other blood disorders	401 (3.4)	244 (3.7)	106 (2.0)	219 (5.1)	970 (3.5)
Infection	682 (5.8)	581 (8.9)	149 (2.8)	262 (6.1)	1674 (6.0)

CRC, colorectal cancer; NHL, non-Hodgkin lymphoma.

antibiotics or CSFs for the prevention of FN. More than half the patients with lung cancer, CRC, or prostate cancer who received primary prophylaxis were given primary prophylactic antibiotics without concomitant CSF (Table 2). In contrast, more than half the patients with NHL who received primary prophylaxis received CSFs alone (Table 2). Among the 12% of patients who received secondary prophylaxis, antibiotics alone were used more commonly in CRC and prostate cancer and CSF alone was used more

Table 2 – FN and supportive care.

Findings	Lung cancer (N = 11,715)	CRC (N = 6549)	Prostate cancer (N = 5322)	NHL (N = 4313)
Overall FN Incidence,* n (%)	1195 (10.2)	302 (4.6)	287 (5.4)	744 (17.3)
Inpatient FN management†	752 (6.4)	147 (2.2)	184 (3.5)	571 (13.2)
Outpatient FN management†	638 (5.5)	188 (2.9)	168 (3.2)	377 (8.7)
Medications, cycle 1, n (%)				
Corticosteroids	9271 (79.1)	2600 (39.7)	3154 (59.3)	3224 (74.8)
Antihistamines	5204 (44.4)	1076 (16.4)	1093 (20.5)	2187 (50.7)
Antiemetics	9909 (84.6)	4337 (66.2)	2419 (45.5)	2880 (66.8)
Primary prophylaxis, n (%)	2656 (22.7)	635 (9.6)	924 (17.4)	1599 (37.1)
Antibiotic only‡	1410 (53.1)	546 (86.0)	709 (76.7)	417 (26.1)
CSF only‡	915 (34.5)	67 (10.6)	173 (18.7)	797 (49.8)
Both CSF and antibiotic,‡,§	331 (12.5)	22 (3.5)	42 (4.6)	385 (24.1)
Duration of prophylaxis (d), mean ± SD	4.6 ± 5.7	6.2 ± 8.4	4.5 ± 5.4	5.0 ± 6.5
Secondary prophylaxis, n (%)	1676 (14.3)	619 (9.5)	452 (8.5)	641 (14.9)
Antibiotic only‖	664 (39.6)	332 (53.6)	241 (53.3)	147 (22.9)
CSF only‖	773 (46.1)	248 (40.1)	157 (34.7)	370 (57.7)
Both CSF and antibiotic§,‖	239 (14.3)	39 (6.3)	54 (12.0)	124 (19.3)
Duration of prophylaxis (d), mean ± SD	5.1 ± 5.0	5.7 ± 4.7	5.1 ± 4.8	4.9 ± 5.2
Reactive use, n (%)	3847 (32.8)	1500 (22.9)	1289 (24.2)	1616 (37.5)
Antibiotic only	2718 (70.7)	1212 (80.8)	1009 (78.3)	793 (49.1)
CSF only	478 (12.4)	164 (10.9)	129 (10.0)	326 (20.2)
Both CSF and antibiotic	651 (16.9)	124 (8.3)	151 (11.7)	497 (30.8)
Duration of reactive use (d), mean ±SD	5.6 (5.6)	5.7 (6.1)	5.9 (5.9)	6.1 (6.4)

CRC, colorectal cancer; CSF, colony-stimulating factor; FN, febrile neutropenia; NHL, non-Hodgkin lymphoma.

* Patient-level incidence.

† If a patient had separate FN episodes that were managed in the inpatient setting and the outpatient setting, then that patient contributed to both inpatient and outpatient FN.

‡ Of those patients who received primary prophylaxis.

‖ Of those patients who received secondary prophylaxis.

§ Either in combination or due to switching.

commonly in lung cancer and NHL. Use of the combination of antibiotics and CSF varied considerably, and these were given most commonly to patients with NHL.

Burden and Consequences of FN

Among patients hospitalized with FN, the mortality rate was 10.0%, 4.8%, 6.5%, and 5.6% for patients with lung cancer, CRC, prostate cancer, and NHL, respectively. Mortality rates were generally higher in the first three chemotherapy cycles versus subsequent cycles, ranging from 4.2% to 12.2% versus 0% to 15.8%, 4.6% to 5.1% versus 0% to 20.0%, 4.4% to 9.2% versus 0% to 6.3%, and 3.2% to 7% versus 0% to 2.3%, respectively.

The mean ± SD inpatient LOS across all cycles was 15.4 ± 15.7, 12.4 ± 13.9, 14.4 ± 16.1, and 9.8 ± 10.4 days for patients with lung cancer, CRC, prostate cancer, and NHL, respectively, and the average inpatient LOS ranged from 5.3 to 13.5, 3.8 to 17.5, 3.0 to 11.0, and 7.1 to 15.1 days, respectively.

The mean ± SD FN-related total medical costs were $17,263 ± $31,562, $17,335 ± $60,644, $13,242 ± $24,115, and $24,571 ± $41,483 for patients with lung cancer, CRC, prostate cancer, and NHL, respectively. Inpatient FN-related costs were higher than outpatient costs for all cancer types: $26,507 ($36,647) versus $1,091 ($1,336), $34,284 ($83,733) versus $1,039 ($1,110), $19,677 ($27,990) versus $1,070 ($1,207), and $31,325 ($45,134) versus $1,046 ($1,192), respectively.

Discussion

This study represents the first detailed description of cancer care and FN within the VHA. The VHA is well suited for epidemiological studies because it includes a large patient population, provides a full continuum of care, uses an all-electronic health record system, and captures extensive detail about patient care in a fully integrated claims database. Furthermore, the VHA has developed a nationwide standard to measure health care value on the basis of cost, access, technical quality, patient's functional ability, and patient satisfaction.

Chemotherapy treatment appeared to be less aggressive within the VHA than recommended by the National Comprehensive Cancer Network guidelines [20–25]. For example, standard of care is a combination chemotherapy regimen consisting of Folinic acid (leucovorin), Fluorouracil (5-FU), and Oxaliplatin (Eloxatin) for CRC and cyclophosphamide, hydroxydaunorubicin (i.e., doxorubicin or Adriamycin), Oncovin (vincristine), and prednisone or prednisolone ± rituximab for NHL; in the VHA, standard-of-care regimens were not frequently observed. Although guidelines recommend that chemotherapy regimens evaluated in this study be administered once every 14 days or once every 21 days, the interval between cycles in the VHA was 39 to 44 days. A number of factors may have contributed to longer cycle durations, including patient preference, physician preference (given the high number of comorbidities in this population), dose delays due to adverse events, less aggressive treatment, a focus on palliative care, inadequate symptom management during the cycle, or a desire to avoid prophylactic CSFs.

Despite the observed differences in chemotherapy regimens and cycle durations, the FN incidence in the VHA (4.6%–17.3%) is similar to that observed in other studies (10%–16.8% [26,27]). Patients with chemotherapy-induced FN are often hospitalized [17]; however, some patients may be at low risk for complications from FN and may be safely treated in the outpatient setting [26,28–30]. In the VHA, approximately half the patients with FN events were managed in the outpatient setting, the exception being patients with NHL. The data suggest that there are either patient subpopulations at low risk of developing FN or that cancer is managed less aggressively within the VHA. In addition, patients within the VHA may have farther to travel to access hospital care and may prefer outpatient care when possible. These patterns of care may delay or hinder access to inpatient care for FN and may result in increased mortality or morbidity.

The burden and consequence of FN in the VHA is generally consistent with other studies [8,10–12,26]. FN-related mortality rates in the VHA versus previous studies were 10.0% versus 10.5% to 21.2%, 4.8% versus 4.8% to 11.2%, and 5.6% versus 5.8% to 19.7% for patients with lung cancer, CRC, and NHL, respectively, with mean LOS of 12.4 days versus 7.1 to 9.5 days, 14.4 days versus 7.2 to 9.6 days, and 15.4 days versus 8.2 to 12.0 days, respectively. Mortality due to FN in later chemotherapy cycles may be lower than that in earlier cycles because few patients received chemotherapy beyond the fourth cycle. In addition, dose reductions, which could not be effectively assessed in this study, would reduce subsequent cycle FN and FN-related outcomes. The longer LOS in the VHA may reflect more complex cases [8,10–12,26].

Total costs were similar at $17,263 versus $17,382 to $17,689, $17,335 versus $19,667, and $24,571 versus $24,218 to $26,208 for patients with lung cancer, CRC, and NHL, respectively [11,12]. Costs among studies should be compared with caution because costs in the current study had wide SDs, likely due to a skewed distribution and the impact of inflation. In addition, VHA costs include slightly different categories than do other payers, such as Medicare [31], and the metric for costs may be set differently than in other health care systems.

The incidence and burden of FN can be affected by patterns of supportive care. For example, nearly 80% of the patients with lung cancer were receiving corticosteroids, potent antipyretics, in cycle 1. Recent guidelines from the American Society of Clinical Oncology and National Comprehensive Cancer Network recommend prophylaxis with antibacterials and antifungals only for patients expected to have severe and prolonged neutropenia and that patients who develop FN should receive prompt antibacterial therapy [15–17]. The American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend primary prophylaxis with CSFs only when the risk of FN is 20% or more, and CSFs are not recommended for treating FN [15,16]. Our study found that only 21% of VHA patients received primary prophylaxis and an additional 12% received secondary prophylaxis. Among patients who received prophylaxis, most received CSF only or antibiotic only; however, up to 24% and 19% received both CSF and antibiotic as primary or secondary prophylaxis, respectively, either in combination or because of switching. The overall relative low use of prophylactic measures in the VHA may be due to regimen modifications to decrease the intensity of chemotherapy because of the presence of comorbidities and advanced-stage disease. In our study, chemotherapy data were insufficient to calculate the actual dose intensity of the treatments given to the patients or to analyze the frequency of treatments having a specific risk of FN of more than 20%.

The current study has some limitations. First, most of the patients within the VHA are elderly men; thus, the results of our study may not be generalizable to the US cancer population. Second, although use of CSFs and/or antibiotics was categorized as prophylactic versus reactive based on timing relative to chemotherapy administration, these agents was unknown. Third, our study was limited to information captured in the electronic medical record and errors of omission and commission may occur. Fourth, overall mortality was not examined, and inpatient mortality does not reflect overall mortality. Fifth, emergency room encounters at a non-VHA facility are not captured in the database, which identifies only the location of encounters with the VA station suffix. Finally, there is no single *ICD-9-CM* code for FN, and the true incidence of FN and FN-related burden can only be approximated using algorithms. Although similar algorithms

have been used to approximate FN in previously published studies [13,14], some patients with severe neutropenia may have been misclassified as having FN.

In summary, patterns of cancer care within the VHA were generally consistent with clinical recommendations. The most notable differences included the aggressiveness of chemotherapy and methods to prevent and treat FN. Many of these differences may be due to the older, frailer patient population served by the VHA.

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Supplemental Materials

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